

REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-19, 21 and 49-66 will be pending in this application and presented for examination. Claims 3-7, 56-57 and 58 have been amended. Claims 20 and 22-48 have been canceled without prejudice or disclaimer. The Examiner has indicated that claims 5, 13-14, 21, 52 and 54-66 contain allowable subject matter. No new matter has been introduced with the foregoing amendments to the claims. Reconsideration is respectfully requested.

I. FORMALITIES

Claims 49-66 have been rejoined with claims 1-21 and examined on their merits. Applicants note that claims 40-50 were previously renumbered 38-48. The specification has been updated with regard to the U.S. Patent Application Number of a related application. Support for the amendments to claims 3-7 and 56-57 is found, for example, on page 7, lines 28-33, bridging to the top of page 8; and on page 8, lines 26-33 bridging to the top of page 9. Finally, claim 58 has been amended to include a comma as suggested by the Examiner. As such, Applicants respectfully request that the amendments be entered.

II. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 6-9 and 20 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In paragraphs 6-7 of the Office Action, the Examiner alleges that claim 6 is indefinite in view of claims 3 and 6. The Examiner states that according to claim 3, the charge switch NP probe is a nucleotide triphosphate (NTP) while, according to claim 6, the NTP probe is selected from the group consisting of a deoxynucleotide triphosphate (dNTP) and a nucleotide triphosphate (NTP). The Examiner alleges in view of claim 3, the NTP of claim 6 is not further limited. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants have amended claims 3, 4, 5, 6, 7, 56 and 57 to more particular point out the subject matter regarded as the invention. In the amendment to claim 3, the NTP portion has been deleted, thus leaving the phrase, "wherein said terminal phosphate is a pyrophosphate with a fluorophore moiety attached thereto." In claim 6, the dependency has been changed such

that claim 6 is now dependent on claim 1. Thus, claim 6 recites that the "charge-switch NP probe is a member selected from the group consisting of a deoxynucleotide triphosphate (dNTP), and a nucleotide triphosphate (NTP)." Claims 4-5, 7, and 56-57 have been amended to recite a NP probe and if applicable, the dependency of the claim has been updated. In view of the amendments to the claims and the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection.

In paragraph 8, the Examiner alleges that claim 20 is indefinite. In response, Applicants have canceled claim 20 without prejudice, thereby rendering this rejection moot.

In view of the foregoing amendments and the cancellation of claim 20, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, second paragraph rejections.

III. FIRST REJECTION UNDER 35 U.S.C. §102

The Examiner has rejected claims 1-2, 10, 19-20, 49-50 and 53 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,001,567 ("Brow *et al.*"). The Examiner alleges that Brow *et al.* teaches detection of nucleic acid sequences by an invader-directed cleavage. The Examiner states that a modified oligonucleotide SEQ ID 61 (5'-Cy3-AminoT-Amino-TCTTTTCACCAGCGAGAC GGG-3') carries a net negative charge. After cleavage with a cleavage enzyme, the following oligonucleotides were generated: 5'-CTTTTCACCAGCGAGAC GGG-3' and 5'-Cy3-AminoT-Amino-T-3'. The Examiner alleges that the longer cleavage fragment carries a net negative charge whereas the smaller cleavage fragment carries a net positive charge. The Examiner further points to Figure 56, example 23, and compounds 70 or 74. In response, Applicants respectfully traverse the rejection.

MPEP §2131 sets forth: A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Brow *et al.* teach at column 17, lines 64-67, bridging to column 18:

[t]he term "oligonucleotide" as used herein is defined as a molecule comprised of **two or more** deoxyribonucleotides or ribonucleotides, preferably at least 5 nucleotides, more preferably at least about 10-

15 nucleotides and more preferably at least about 15 to 30 nucleotides. The exact size will depend on many factors, which in turn depends on the ultimate function or use of the oligonucleotide. The oligonucleotide may be generated in any manner, including chemical synthesis, DNA replication, reverse transcription, or a combination thereof. [Emphasis added].

Brow *et al.* teach that the oligonucleotides, which are complementary to the target nucleic acid, must be comprised of at least **two or more** single nucleotides. The oligonucleotides of Brow *et al.* **hybridize** to a target nucleic acid. Brow *et al.* state that the "exact size will depend on many factors, which in turn depends on the ultimate function or use of the oligonucleotide." However, the exact size is at least **two or more** single nucleotides.

In stark contrast, the present invention provides a "charge-switch nucleotide phosphate (NP) probe". The NP probe is **a single monomer**, having a single base, a single sugar and a least one phosphate group. The term nucleotide is defined on page 8, bridging to the top of page 9 as follows:

The term "**nucleotide**" as used herein refers to a phosphate ester of a nucleoside, e.g., mono, di and triphosphate esters, wherein the most common site of esterification is the hydroxyl group attached to the C-5 position of the pentose. Nucleosides also include, but are not limited to, synthetic nucleosides having modified base moieties and/or modified sugar moieties, e.g. described generally by Scheit, Nucleotide Analogs (John Wiley, N.Y., 1980). Suitable NTPs include both naturally occurring and synthetic nucleotide triphosphates, and are not limited to, ATP, dATP, CTP, dCTP, GTP, dGTP, TTP, dTTP, UTP and dUTP. Preferably, the nucleotide triphosphates used in the methods of the present invention are selected from the group of dATP, dCTP, dGTP, dTTP, dUTP and mixtures thereof.

The terms "a charge-switch nucleotide phosphate (NP) probe," "a NP probe" and "a charge-switch nucleotide" are used interchangeably and are defined on page 7, bridging to the top of page 8:

The term "charge-switch **nucleotide**" as used herein refers to a labeled **nucleotide** phosphate (e.g., γ -NP-Dye) that upon release or cleavage of a phosphate detectable moiety (e.g., PPi-Dye) has a different net charge associated with the cleavage product compared to the intact nucleotide phosphate probe (e.g., γ -NP-Dye). In certain preferred aspects, the attachment of the dye to the PPi is via a

nitrogen in lieu of an oxygen. Preferably, the charge difference between the intact γ -NP-Dye and the PPI-Dye is at least 0.5, and more preferably about 1 to about 4 (e.g., 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, and 4.0).

Under MPEP §2131, a claim is anticipated *only if* each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Brow *et al.* teaches an oligonucleotide as a molecule comprised of **two or more** deoxyribonucleotides or ribonucleotides. The oligonucleotides of Brow *et al.* are structurally different and are used for an entirely different purpose than the charge-switch nucleotides of the present invention.

Likewise, compounds 70 and 74 depicted in Figure 56, contain **two** amino modified thymidines. The Examiner correctly points this out on page 7, of the Office Action, wherein it is stated: [a]s shown in Figure 56 and Example 23, compounds 70 or 74 contained **two** amino modified thymidines that..." [Emphasis added].

As the term "charge-switch nucleotide" as used herein refers to a single nucleotide phosphate, Applicants respectfully request that the Examiner withdraw the anticipation rejection.

IV. SECOND REJECTION UNDER 35 U.S.C. §102

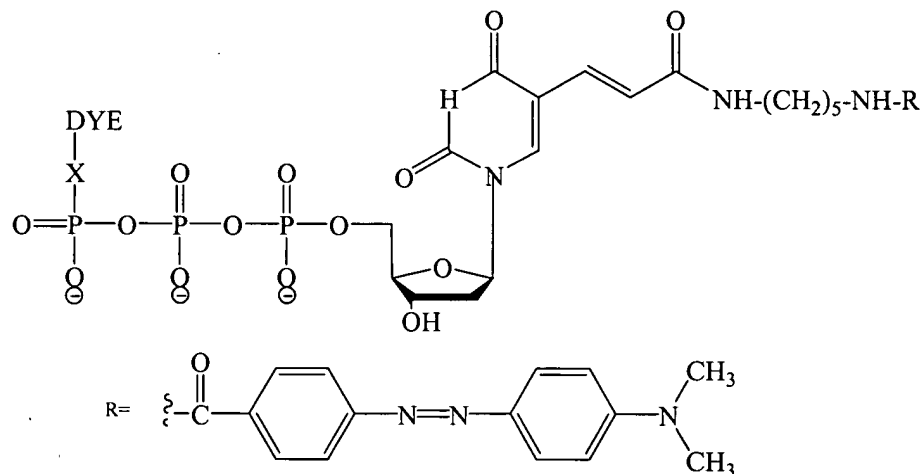
The Examiner has rejected claims 1-4, 6-12 and 15-20 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,232,075 ("Williams"). The Examiner alleges that Williams teach a heterogeneous assay for pyrophosphate detection. Figure 4 allegedly teaches a dNTP attached to a fluorophore. The Examiner then continues by saying that "[s]ince various different fluorescence dyes such as Cy3 or Cy5 are used as the fluorophore moiety and the quencher moiety in the labeled dNTP (see columns 12 and 13), **here we assume that, in the dNTP in Figure 4, its fluorophore moiety does not bear any charge and the quencher moiety is Cy3.**" [Emphasis in the original]. "Since it is known that cy3 is a fluorescent dye carrying a net single positive charge (see page 2, last paragraph of the attachment for CyDye). This moiety allegedly carries a positive charge of -2." The Examiner states that this moiety would have a cleavage product having a net charge of -3. Therefore, the Examiner alleges that

Williams anticipates the present invention. In response, Applicants respectfully traverse the rejection.

Applicants assert that Williams does not anticipate the present invention. In this regard, the Examiner's attention is respectfully directed to column 18, lines 10-17, of Williams. As stated therein,

[t]his Example illustrates the synthesis of γ -phosphate modified dNTP's with linkers. DABCYL-dNTP Synthesis DABCYL-succinimidyl ester (see, FIG. 3, Molecular Probes, Inc.) is conjugated to 5-allylamino dUTP (see, FIG. 4). The synthesized compound is used to screen for polymerases able to incorporate DABCYL at every base.

Thus, Williams teaches Figure 4 is DABCYL-succinimidyl ester conjugated to 5-allylamino dUTP. DABCYL is the abbreviation for 4-(dimethylaminoazo)benzene-4-carboxylic acid. With reference to Figures 3 and 4 of Williams, this reference teaches attaching a DABCYL on a uracil.



It is respectfully submitted that the Examiner is not permitted to "assume that the dNTP in Figure 4, the fluorophore moiety does not bear any charge and the quencher is CY-3," without an express or inherent description of such a molecule. Applicants respectfully point out that the reference must anticipate the application without any additional assumption made by the Examiner. Again, Williams teaches at column 18, lines 10-17, [t]his Example illustrates the synthesis of γ -phosphate modified dNTP's with linkers. DABCYL-dNTP Synthesis DABCYL-succinimidyl ester (see, FIG. 3, Molecular Probes, Inc.) is conjugated to 5-allylamino dUTP (see,

FIG. 4). Without the Examiner's assumption, this simply does not anticipate the claims. Accordingly, Applicants request that the Examiner withdraw the anticipation rejection.

V. THIRD REJECTION UNDER 35 U.S.C. §102

The Examiner has rejected claims 1-4, 6-12 and 15-20 under 35 U.S.C. § 102(f) as allegedly the Applicant did not invent the claimed subject matter. The Examiner alleges that the Williams patent has a single inventor, whereas the subject application has additional inventors. In response, Applicants respectfully traverse the rejection.

In this action, Applicants have canceled without prejudice claims 20 and 22-48. In so doing, Applicants have submitted a Petition under 37 CFR § 1.48(b) to amend the inventorship. However, there are still more inventors of the subject application compared to U.S. Patent No. 6,232,075.

Applicants submit that the inventorship of U.S. Patent No. 6,232,075 is correct. Further, Applicants submit that the inventorship of the subject application is correct. In view of remarks set forth in section IV above, it is clear that U.S. Patent No. 6,232,075 does not anticipate the present claims. Further, claims 1-19, 21 and claims 49-66 are pending in the present application, whereas the Examiner has rejected *only* claims 1-4, 6-12 and 15-20 under 35 U.S.C. §102(f). In certain instances, the contribution of inventors other than John G.K. Williams, is embodied in claims other than rejected claims 1-4, 6-12 and 15-20. As such, Applicants respectfully request that the Examiner withdraw the rejection.

VI. DOUBLE PATENTING

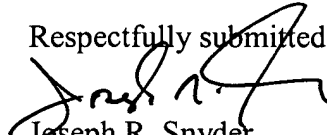
Claims 1-4, 6-12 and 18-20 were rejected as allegedly being obvious over claims 12-28 of U.S. Patent No. 6,232,075. Applicants respectfully request that the Examiner hold this rejection in abeyance until all the subject matter of the present invention is in condition for allowance. At that time, Applicants will take the necessary steps to obviate the double patenting rejection.

VII. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300

JS:js
60123757 v1